4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-N-1400]

Complex Innovative Design Paired Meeting Program

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The seventh iteration of the Prescription Drug User Amendments (PDUFA VII), included as part of the FDA User Fee Reauthorization Act of 2022, highlights the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs. The Food and Drug Administration (FDA or Agency) is announcing the continuation of the paired meeting program established under the sixth iteration of PDUFA that affords sponsors, who are selected, the opportunity to meet with Agency staff to discuss the use of complex innovative trial design (CID) approaches in medical product development. Meetings under the program will be conducted by FDA's Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) during fiscal years 2023 to 2027. For each sponsor whose meeting request is granted, two meetings will be held between the sponsor and CDER or CBER that will provide an opportunity for medical product developers to discuss their CID proposals. To promote innovation in this area, trial designs developed through the paired meeting program may be presented by FDA (e.g., in a guidance or public workshop) as case studies, including trial designs for drugs that have not yet been approved by FDA.

DATES: The CID Paired Meeting Program will proceed from October 1, 2022, through September 30, 2027. Sponsors may submit meeting requests for the program through June 30, 2027. Either electronic or written comments about this meeting program must be submitted by November 3, 2022.

ADDRESSES: You may submit comments about the CID paired meetings program as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 3, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked, and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2022-N-1400 for "Complex Innovative Design Paired Meeting Program." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket

number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: *CDER*: Scott Goldie, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-796-2055, Scott.Goldie@fda.hhs.gov, with the subject line "CID Paired Meeting Program for CDER."

CBER: Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

In connection with the seventh iteration of PDUFA, FDA committed to continue the paired meeting program established under PDUFA VI for highly innovative trial designs, with a particular focus on trial designs for which simulations are necessary to evaluate the trial operating characteristics. The Agency also committed to issue a *Federal Register* notice announcing the continuation of the paired meeting program, outlining program eligibility, and describing the proposal submission, selection process, and example topics that will advance the use of complex innovative designs and inform the development of a guidance document (see PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027, section I.L.4.b, https://www.fda.gov/media/151712/download).

FDA is announcing the continuation of the paired meeting program to satisfy the above-mentioned commitments. The goals of the early meeting discussions granted under this program are to provide advice on how a proposed CID approach can be used in a specific drug development program and to promote innovation by allowing FDA to publicly present the trial

designs considered through the program, including trial designs for drugs that have not yet been approved by FDA. FDA has committed to accepting up to eight proposals each fiscal year.

Meeting requests may be submitted on a rolling basis; however, only those received by the quarterly closing date, which will be the last day of each quarter of the fiscal year (i.e., December 31, March 31, June 30, September 30), will be considered for selection in the following quarter. Within 45 days after the quarterly closing date, FDA will review the submissions, select meeting requests to proceed to disclosure discussions, and notify sponsors of their status. When disclosure discussions are complete, FDA will grant the paired meetings request.

The Meeting Request Granted letter will include the date for an initial meeting. The follow-up meeting will occur approximately 90 days after receiving the follow-up meeting package. Being granted a meeting as part of the paired meeting program does not mean that the proposed CID is appropriate for regulatory decision making. Likewise, being denied a meeting as part of the paired meeting program does not mean that the proposed CID is unacceptable for regulatory decision making. Sponsors who do not participate in the paired meeting program may seek Agency interaction on their clinical development plan through traditional channels (e.g., Type C meeting requests, Critical Path Innovation Meetings).

The listed eligibility factors and procedures outlined in this notice reflect the current thinking at the time of publication. Processes may be revised and will be communicated on the following web page: https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program.

II. Eligibility and Selection for Participation in the CID Paired Meeting Program

To be eligible for the CID Paired Meeting Program:

- The sponsor must have a pre-investigational new drug (IND) application or IND number for the medical product(s) included in the CID meeting request with the intent of implementing the CID proposed in the meeting request.

- The trial is not a first in human study, and there is sufficient clinical information available to inform the proposed CID.
- The sponsor and FDA are able to reach agreement on the trial design information to be publicly disclosed.

Example CIDs include, but are not limited to:

- Trials with adaptations to multiple design features such as treatment arm selection or patient allocation.
- Formal incorporation of prior information such as placebo augmentation using an external control or other data sources, or other approaches to leverage information internal or external to the trial.
- Use of posterior probability or decision-theoretic approaches to determine trial success criteria.
- Trials with novel application of complex design features for a given indication (even when those design features have been used in other indications), such as use of an active-controlled, non-inferiority design in a setting where placebo-controlled designs have typically been used and where there is a novel or complex approach for determining the non-inferiority margin.
- Master protocols.
- Sequential multiple assignment randomized trial designs.

The Agency currently plans to accept requests based on the following:

- Innovative features of the trial design, particularly if the innovation may provide advantages over alternative approaches.
- Therapeutic need (i.e., therapies being developed for use in disease areas where there are no or limited treatment options).

- Priority will be given to trial designs for which analytically derived properties (e.g., Type I error) may not be feasible and simulations are necessary to determine operating characteristics.
- Priority will also be given to proposed CIDs intended to provide substantial evidence of effectiveness to support regulatory approval of the medical product.

III. Procedures and Submission Information

A. General Information

The CID Paired Meeting Program will be jointly administered by the following Centers:

- *CDER*: CDER's Office of Biostatistics, in the Office of Translational Sciences, which is the point of contact for CID Paired Meeting Program communications for CDER products.
- *CBER*: CBER's Division of Biostatistics, in the Office of Biostatistics and Pharmacovigilance, which is the point of contact for CID Paired Meeting Program communications for CBER products.

B. How to Submit a Meeting Request and Meeting Package

Meeting requests should be submitted electronically to the relevant application (*i.e.,* Pre-IND, IND) with "CID Program Meeting Request for CDER" (CDER applications) or "CID Program Meeting Request for CBER" (CBER applications) in the subject line. Information about providing regulatory submissions in electronic format is available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

C. Content and Format of the Meeting Request

Include the following information in the meeting request (25 pages or less):

1. Product Name.
2. Application Number.
3. Proposed indication(s) or context of product development.

4. A background section that provides a brief history of the development program and the status of product development.

5. Trial objectives.

6. Brief rationale for the choice of the proposed CID.

7. Description of study design, including study schema with treatment arms, randomization strategy, and endpoints.

8. Key features of the statistical analysis plan including, but not limited to, the analyses, model, analysis population, approach to handle missing data, and decision criteria. These should include aspects of the design that may be modified and the corresponding rules for decisions, if adaptive.

9. Simulation plan, including the set of parameter configurations that will be used for the scenarios to be simulated and preliminary evaluation and discussion of design operating characteristics. Preliminary simulation results of the operating characteristics (e.g., Type I error, power, etc.) should include several hypothetical plausible scenarios.

10. Elements of the study design that the sponsor considers non-disclosable, along with a rationale for exclusion.

11. A list of issues for discussion with the Agency about the specific proposed CID approach for the applicable drug development program.

D. Content and Format of the Meeting Information Package

Sponsors whose meeting requests are granted as part of the program should submit a meeting information package electronically with "CID Paired Meeting Program Package for CDER" (CDER applications) or "CID Paired Meeting Program Package for CBER" (CBER applications) in the subject line.

The initial meeting package should include the following information:

1. Product name.

2. Application number.

3. Proposed agenda, including estimated time needed for discussion of each agenda item.

4. List of questions for discussion along with a brief summary of each question that explains the need or context for the question.

5. Detailed description of the statistical methodology including, but not limited to, the analyses, model, analysis population, approach to handle missing data, and decision criteria.

6. Detailed simulation report that includes the following:

    a. Example trials in which a small number of hypothetical trials are described with different conclusions.

    b. Description of the set of parameter configurations used for the simulation scenarios, including a justification of the adequacy of the choices.

    c. Simulation results, including operating characteristics such as Type I error probability, power, expected sample size/duration, and estimation properties under various scenarios.

    d. Simulation code that is readable, adequately commented on, and includes the random seeds. The code should preferably be written in widely used programming languages such as R or SAS to facilitate the simulation review.

    e. Overall conclusions, including a brief summary of the simulated operating characteristics based on the design features and analyses and a discussion of the utility of the CID given the simulation results.

The followup meeting package should include the following information:

1. Product name.

2. Application number.

3. Updated background section that includes a brief history of the development program and the status of product development and clinical data to date, if applicable.

4. Proposed agenda, including estimated times needed for discussion of each agenda item.

5. List of questions for discussion along with a brief summary of each question that explains the need or context for the question.

6. Updated programs/shells for simulations, if applicable.

7. Summary of new information that is available to support discussions.

E. Meeting Summary

A meeting summary will be sent to the sponsor within 60 days of each meeting.

F. Disclosure

To promote innovation in this area, trial designs developed through the paired meeting program may be presented by FDA (e.g., in a guidance, at public workshops and conferences, or on FDA's website) as case studies, including while the drug studied in the trial has not yet been approved by FDA. Accordingly, before FDA grants the initial meeting under the program, FDA and the sponsor must agree on the information that FDA may include in these public case studies. The specific information to be disclosed will depend on the content of each CID proposal, but FDA intends to focus on information that is beneficial to advancing the use of CIDs, and those elements relevant to understanding of the CID and its potential use in a clinical trial intended to support regulatory approval. Generally, the Agency does not anticipate that the case studies will need to include information such as molecular structure, the sponsor's name, product name, subject-level data, recruitment strategies, or a complete description of study eligibility criteria. FDA does anticipate that the following information will generally be disclosed to facilitate discussion of the proposed CID:

1. Rationale for the selected design.
2. Study design characteristics:
    a. Randomization.
    b. Blinding.
    c. Study schema.
    d. Study endpoints.
    e. Target population.
    f. Sample size determination, including assumptions.
    g. Choice of controls (external/historical, concurrent).

h. Estimand(s) of interest.

i. Adaptive elements, including aspects of the design that can be modified.

3. Analysis plan:

   a. Model(s), including underlying assumptions and any prior distributions.

   b. Null and alternative hypotheses.

   c. Statistical test(s).

   d. Approaches to handle missing data and multiplicity.

   e. Decision criteria throughout the trial, including rules for adaptive decisions.

4. Simulations:

   a. Objectives and assumptions.

   b. Scenarios, including parameter configurations and the rationale for parameter values considered, and hypothetical examples of trials for a given simulation scenario.

   c. Simulation results, including operating characteristics such as Type I error probability, power, expected sample size/duration, and estimation properties.

5. Data access plan components and any other approaches to minimize impacts on trial integrity imposed by the innovative design.

6. Any modifications or amendments to any of the above that occur during interactions about the proposed CID between Submitter and FDA.

It is important that sponsors wishing to participate in the program identify aspects of the design and analysis that they consider non-disclosable and provide a rationale for withholding the information. Participation in the program, including any agreement on information disclosure, will be voluntary and at the discretion of the sponsor. Sponsors that do not wish to make such disclosures may seek regulatory input through other existing channels.

IV. Paperwork Reduction Act of 1995

This notice refers to collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-

3521). The collection of information resulting from formal meetings between sponsors or applicants and FDA has been approved under OMB control number 0910-0429. The collection of information in 21 CFR part 312 (investigational new drug applications) has been approved under OMB control number 0910-0014.

Dated: October 17, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

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